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suppression of the thyroid (Wolff-Chaikoff effect), and the inhibitory effects on deiodinase activity and thyroid hormone receptor action become predominant. These events lead to the following pattern of thyroid function tests: increased T4, decreased T3, increased rT3, and a transient TSH increase (up to 20 mIU/L). TSH levels normalize or are slightly suppressed within 1–3 months.

The incidence of hypothyroidism from amiodarone varies geo graphically, apparently correlating with iodine intake. Hypothyroidism occurs in up to 13% of amiodarone-treated patients in iodine-replete countries, such as the United States, but is less common (<6% inci dence) in areas of lower iodine intake, such as Italy or Spain. The pathogenesis appears to involve an inability of the thyroid gland to escape from the Wolff-Chaikoff effect in autoimmune thyroiditis. Consequently, amiodarone-associated hypothyroidism is more com mon in women and individuals with positive TPO antibodies. It is usually unnecessary to discontinue amiodarone for this side effect, because LT4 can be used to normalize thyroid function. TSH levels should be monitored, because T4 levels are often increased for the rea sons described above. In addition, TSH levels need to be monitored in LT4-replaced hypothyroid patients because a dosage increase is often required. PART 12 Endocrinology and Metabolism The management of amiodarone-induced thyrotoxicosis (AIT) is complicated by the fact that there are different causes of thyrotoxicosis and because the increased thyroid hormone levels exacerbate underly ing arrhythmias and coronary artery disease. Amiodarone treatment causes thyrotoxicosis in 10% of patients living in areas of low iodine intake and in 2% of patients in regions of high iodine intake. There are two major forms of AIT, although some patients have features of both. Type 1 AIT is associated with an underlying thyroid abnormal ity (preclinical Graves' disease or nodular goiter). Thyroid hormone synthesis becomes excessive as a result of increased iodine exposure (Jod-Basedow phenomenon). Type 2 AIT occurs in individuals with no intrinsic thyroid abnormalities and is the result of drug-induced lyso somal activation leading to destructive thyroiditis with histiocyte accu mulation in the thyroid; the incidence rises as cumulative amiodarone dosage increases. Mild forms of type 2 AIT can resolve spontaneously or can occasionally lead to hypothyroidism. Color-flow Doppler ultra sonography shows increased vascularity in type 1 AIT but decreased vascularity in type 2 AIT. Thyroid scintiscans are difficult to interpret in this setting because the high endogenous iodine levels diminish tracer uptake. However, the presence of normal or rarely increased uptake favors type 1

AIT. In AIT, because of amiodarone’s prolonged half-life and storage in adipose tissue, there is no immediate benefit from discontinuing the drug. Treatment studies have reported a similar time course for AIT type 2 resolution whether amiodarone was continued or stopped. Therefore, the decision to discontinue the drug should be based upon the severity of the arrhythmia. High doses of antithyroid drugs can be used in type 1 AIT but are often ineffective. Potassium perchlorate, 500 mg bid, has been used to reduce thyroidal iodide content. Perchlorate treatment has been associated with agranulocytosis, although the risk appears relatively low with short-term use. This drug is also no longer available in many countries. Glucocorticoids (initial dose usually 40–60 mg/d of prednisone) are effective in treating in type 2 AIT. Near-total thyroid ectomy rapidly decreases thyroid hormone levels and may be the most effective long-term solution if the patient can undergo the procedure safely. ■ ■FURTHER READING Alexander EK et al: 2017 Guidelines of the American Thyroid Asso ciation for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 27:315, 2017. Biondi B, Cooper DS: Subclinical hyperthyroidism. N Engl J Med 378:2411, 2018. Burch HB et al: Management of thyroid eye disease: A Consensus Statement by the American Thyroid Association and European Thyroid Association. Thyroid 32:1439, 2022. Kim BW: Does radioactive iodine therapy for hyperthyroidism cause cancer? J Clin Endocrinol Metab 107:e448, 2022.

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J. Larry Jameson

Thyroid Nodular Disease

and Thyroid Cancer ■ ■GOITER AND THYROID NODULAR DISEASE Goiter refers to an enlarged thyroid gland. Biosynthetic defects, iodine deficiency, autoimmune disease, and nodular diseases can each lead to goiter, although by different mechanisms. Biosynthetic defects and iodine deficiency are associated with reduced efficiency of thyroid hormone synthesis, leading to increased thyroid-stimulat ing hormone (TSH), which stimulates thyroid growth as a compensa tory mechanism to overcome the block in hormone synthesis. Graves’ disease and Hashimoto’s thyroiditis are also associated with goiter. In Graves’ disease, the goiter results mainly from the TSH-R–medi ated effects of thyroid-stimulating immunoglobulins. The goitrous form of Hashimoto’s thyroiditis occurs because of acquired defects in hormone synthesis, leading to elevated levels of TSH and its con sequent growth effects. Lymphocytic infiltration and immune sys tem–induced growth factors also contribute to thyroid enlargement in Hashimoto’s thyroiditis. Thyroid nodular disease is characterized by the disordered growth of thyroid cells, which can be either hyperplastic or neoplastic. A patient may have a multinodular goiter (MNG) in which thyroid nodules (generally hyperplastic) replace the majority of the normal thyroid parenchyma; this presentation is more common in areas of borderline iodine deficiency. Or, the thyroid gland may be normal in size and contain discrete thyroid nodules. Because the management of goiter depends on the etiology, the detection of thyroid enlarge ment on physical examination should prompt further evaluation to identify its cause. Nodular thyroid disease is common, occurring in about 3–7% of adults when assessed by physical examination. Using ultrasound, nod ules are present in up to 50% of adults,

with the majority being <1 cm in diameter. Thyroid nodules may be solitary or multiple, and they may be functional or nonfunctional. ■ ■DIFFUSE NONTOXIC (SIMPLE) GOITER Etiology and Pathogenesis When diffuse enlargement of the thyroid occurs in the absence of nodules and hyperthyroidism, it is referred to as a diffuse nontoxic goiter. This is sometimes called simple goiter and is characterized by the presence of uniform follicles that are filled with colloid. Worldwide, diffuse goiter is most commonly caused by iodine deficiency and is termed endemic goiter when it affects >5% of the population. In nonendemic regions, sporadic goiter occurs, and the cause is usually unknown. Thyroid enlargement in teenagers is sometimes referred to as juvenile goiter. In general, goiter is more com mon in women than men, probably because of the greater prevalence of underlying autoimmune disease and the increased iodine demands associated with pregnancy.

In iodine-deficient areas, thyroid enlargement reflects a compen satory effort to trap iodide and produce sufficient hormone under conditions in which hormone synthesis is relatively inefficient. Somewhat surprisingly, TSH levels are usually normal or only slightly increased, suggesting increased sensitivity to TSH or activa tion of other pathways that lead to thyroid growth. Iodide appears to have direct actions on thyroid vasculature and may indirectly affect growth through vasoactive substances such as endothelins and nitric oxide. Endemic goiter may also be caused by exposure to environmental goitrogens such as cassava root, which contains a thiocyanate; vegetables of the Cruciferae family (known as crucifer ous vegetables) (e.g., Brussels sprouts, cabbage, and cauliflower); and milk from regions where goitrogens are present in grass. Although relatively rare, inherited defects in thyroid hormone synthesis lead to a diffuse nontoxic goiter. Abnormalities at each step of hormone syn thesis, including iodide transport (sodium/iodide symporter [NIS]), thyroglobulin (Tg) synthesis, organification and coupling (thyroid peroxidase [TPO]), and the regeneration of iodide (dehalogenase), have been described. ■ ■CLINICAL MANIFESTATIONS AND DIAGNOSIS If thyroid function is preserved, most goiters are asymptomatic. Exami nation of a diffuse goiter reveals a symmetrically enlarged, nontender, generally soft gland without palpable nodules. Goiter is defined, some what arbitrarily, as a lateral lobe with a volume greater than the thumb of the individual being examined. On ultrasound, total thyroid volume exceeding 30 mL is considered abnormal. If the thyroid is markedly enlarged, it can cause tracheal or esophageal compression. These features are unusual, however, in the absence of nodular disease and fibrosis. Substernal goiter may obstruct the thoracic inlet. Pemberton’s sign refers to facial and neck congestion due to jugular venous obstruc tion when the arms are raised above the head, a maneuver that draws the thyroid into the thoracic inlet. Respiratory flow measurements and computed tomography (CT) or magnetic resonance imaging (MRI) should be used to evaluate substernal goiter in patients with obstructive signs or symptoms. Thyroid function tests should be performed in all patients with goiter to exclude thyrotoxicosis or hypothyroidism. It is not unusual, particularly in iodine deficiency, to find a low total T4, with normal T3 and TSH, reflecting enhanced T4 → T3 conversion, as well as preferential T3 production. A low TSH with a normal free T3 and free T4, particularly in older patients, suggests the possibility of thyroid autonomy or undiagnosed Graves’ disease, and is termed subclinical thyrotoxicosis. The benefit of treatment (typically with radioiodine) in subclinical thyrotoxicosis, versus follow-up and implementing treatment if free T3 or free T4 levels become abnormal, is unclear, but treatment is increasingly recommended in the elderly to reduce the risk of atrial fibrillation and bone loss. Low urinary iodine levels

(<50 µg/L) support a diagnosis of iodine deficiency. Thyroid scanning is not generally necessary for euthyroid patients. If preformed, scintig raphy demonstrates increased uptake in iodine deficiency

and most cases of dyshormonogenesis. TREATMENT Diffuse Nontoxic (Simple) Goiter Iodine replacement induces variable regression of goiter in iodine deficiency, depending on duration and the degree of hyperplasia, with accompanying fibrosis, and autonomous function that may have developed. Surgery is rarely indicated for diffuse goiter. Exceptions include documented evidence of tracheal compres sion or obstruction of the thoracic inlet, which are more likely to be associated with substernal MNGs (see below). Subtotal or near-total thyroidectomy for these or cosmetic reasons should be performed by an experienced surgeon to minimize complication rates. Surgery should be followed by replacement with levothy roxine (LT4).

■ ■NONTOXIC MULTINODULAR GOITER

Etiology and Pathogenesis Depending on the population stud ied, MNG or the presence of nodules in a thyroid of normal size occurs in up to 12% of adults. MNG should be distinguished from the presence of nodules in a normal-size thyroid gland (see “Approach to the Patient with Thyroid Nodules”). MNG is more common in women than men and increases in prevalence with age. It is more common in iodine-deficient regions but also occurs in regions of iodine sufficiency, reflecting multiple genetic, autoimmune, and environmental influences on the pathogenesis. Thyroid Nodular Disease and Thyroid Cancer CHAPTER 397 There is typically wide variation in nodule size. Histology reveals a spectrum of morphologies ranging from hypercellular, hyperplastic regions to cystic areas filled with colloid. Fibrosis is often extensive, and areas of hemorrhage or lymphocytic infiltration may be seen. Using molecular techniques, most nodules within an MNG are poly clonal in origin, suggesting a hyperplastic response to locally produced growth factors and cytokines. TSH, which is usually not elevated, may play a permissive or contributory role. Monoclonal neoplastic lesions may also occur, reflecting mutations in genes that confer a selective growth advantage to the progenitor cell. Clinical Manifestations Most patients with nontoxic MNG are asymptomatic and euthyroid. MNG typically develops over many years and is detected on routine physical examination, when an individual notices an enlargement in the neck, or as an incidental finding on imag ing. If the goiter is large enough, it can ultimately lead to compressive symptoms including difficulty swallowing, respiratory distress (tracheal compression), or plethora (venous congestion), but these symptoms are uncommon. Symptomatic MNGs are usually large and/or develop fibrotic areas that cause compression. Sudden pain in an MNG is usually caused by hemorrhage into a nodule. Hoarseness, reflecting laryngeal nerve involvement, may suggest malignancy but more commonly is due to others causes such as gastroesophageal reflux. Diagnosis On examination, thyroid architecture is distorted, and multiple nodules of varying size can be appreciated. Because many nodules are deeply embedded in thyroid tissue or reside in posterior or substernal locations, it is not possible to palpate all nodules. Pem berton’s sign, characterized by facial suffusion when the patient’s arms are elevated above the head, suggests that the goiter has increased pressure in the thoracic inlet. A TSH level should be measured to exclude subclinical hyper- or hypothyroidism, but thyroid function is usually normal. Tracheal deviation is common, but compression must usually exceed 70% of the tracheal diameter before there is significant airway compromise. Pulmonary function testing can be used to assess the functional effects of compression, which characteristically causes inspiratory stridor. CT or MRI can be used to evaluate the anatomy of the goiter and the extent of substernal extension or tracheal nar rowing. A barium swallow may reveal the extent of esophageal com pression. The risk of malignancy in MNG is similar to that in solitary nodules. Ultrasonography should be used to identify which nodules should be biopsied based on a combination of size and sonographic pattern (Fig. 397-1) (Chap. 394). For nodules with more

suspicious sonographic patterns (e.g., hypoechoic solid nodules with irregular borders), biopsy is recommended at a lower size cutoff than those with less suspicious imaging features (Figs. 397-1 and 397-2). TREATMENT Nontoxic Multinodular Goiter Most nontoxic MNGs can be managed conservatively. T4 sup pression is rarely effective for reducing goiter size and introduces the risk of subclinical or overt thyrotoxicosis, particularly if there is underlying autonomy or if it develops during treatment. Contrast agents and other iodine-containing substances should be avoided because of the risk of inducing the Jod-Basedow effect, characterized by enhanced thyroid hormone production by autonomous nodules. Radioiodine has been used when surgery

ACR TI-RADS COMPOSITION ECHOGENICITY (Choose 1) (Choose 1) Cystic or almost
0 points completely cystic Anechoic
0 points Wider-than-tall
0 points Hyperechoic or
1 point isoechoic Taller-than-wide
3 points Spongiform
0 points Mixed cystic
1 point and solid Hypoechoic
2 points Very hypoechoic
3 points Solid or almost
2 points completely solid PART 12 Endocrinology and Metabolism Add Points From All Categories to Determine TI-RADS Level 0 Points 2 Points TR1 Benign No FNA TR2 Not Suspicious No FNA TR3 Mildly Suspicious FNA if ≥ 2.5 cm Follow if ≥ 1.5 cm COMPOSITION ECHOGENICITY SHAPE MARGIN ECHOGENIC FOCI Anechoic: Applies to cystic or almost completely cystic nodules. Taller-than-wide: Should be assessed on a transverse image with measurements parallel to sound beam for height and perpendicular to sound beam for width. Spongiform: Composed predominantly (>50%) of small cystic spaces. Do not add further points for other categories. Hyperechoic/isoechoic/hypoechoic: Compared to adjacent parenchyma. Mixed cystic and solid: Assign points for predominant solid component. Very hypoechoic: More hypoechoic than strap muscles. This can usually be assessed by visual inspection. Assign 1 point if echogenicity cannot be determined. Assign 2 points if composition cannot be determined because of calcification. *Refer to discussion of papillary microcarcinomas for 5-9 mm TR5 nodules. FIGURE 397-1 American College of Radiology (ACR) Thyroid Imaging Reporting and Data System (TI-RADS). TI-RADS is a five-tiered system categorizing the sonographic appearance of thyroid nodules based on increased risk for malignancy. For each level (TR1–5), there are recommendations for both fine-needle aspiration (FNA) minimum size cutoffs and follow-up. (Reproduced with permission from FN Tessler et al: ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee. J Am Coll Radiol 14:587, 2017.) is contraindicated in areas where large nodular goiters are more prevalent (e.g., some areas of Europe and Brazil) because it can decrease MNG volume and may selectively ablate regions of autonomy. Dosage of 131I depends on the size of the goiter and radioiodine uptake but is usually about 3.7 MBq (0.1 mCi) per gram of tissue, corrected for uptake (typical dose 370–1070 MBq [10–29 mCi]). Repeat treatment may be needed, and effective ness may be increased by concurrent administration of low-dose recombinant TSH (0.1 mg IM). It is possible to achieve a 40–50% reduction in goiter size in most patients. Earlier concerns about radiation-induced thyroid swelling and tracheal compression have diminished, as studies have shown this complication to be rare. When acute compression occurs, glucocorticoid treatment or surgery may be needed. Radiation-induced hypothyroidism is less common than after treatment for Graves’ disease.

However, posttreatment autoimmune thyrotoxicosis may occur in up to 5% of patients treated for nontoxic MNG. Surgery remains highly effective but is not without risk, particularly in older patients with underlying cardiopulmonary disease. ■ ■TOXIC MULTINODULAR GOITER The pathogenesis of toxic MNG appears to be similar to that of nontoxic MNG; the major difference is the presence of functional autonomy in toxic MNG. The molecular basis for autonomy in toxic MNG remains unknown. As in nontoxic goiters, many nodules are polyclonal, whereas others are monoclonal and vary in their clonal

SHAPE (Choose 1) MARGIN (Choose 1) ECHOGENIC FOCI (Choose All That Apply) Smooth
0 points None or large
0 points comet-tail artifacts Ill-defined
0 points Macrocalcifications
1 point Lobulated or
2 points irregular Peripheral (rim) 2 points calcifications Extra-thyroidal
3 points extension Punctate echogenic 3 points foci 4 to 6 Points 7 Points or More 3 Points TR4 Moderately Suspicious FNA if ≥ 1.5 cm Follow if ≥ 1 cm TR5 Highly Suspicious FNA if ≥ 1 cm Follow if ≥ 0.5 cm* Large comet-tail artifacts: V-shaped, >1 mm, in cystic components. Lobulated: Protrusions into adjacent tissue. Irregular: Jagged, spiculated, or sharp angles. Macrocalcifications: Cause acoustic shadowing. Extrathyroidal extension: Obvious invasion = malignancy. Peripheral: Complete or incomplete along margin. Assign 0 points if margin cannot be determined. Punctate echogenic foci: May have small comet-tail artifacts. origins. Genetic abnormalities known to confer functional autonomy, such as activating TSH-R or GSα mutations (see below), are not usually found in the autonomous regions of toxic MNG goiter. In addition to features of goiter, the clinical presentation of toxic MNG includes subclinical or mild overt hyperthyroidism. The patient is usually elderly and may present with atrial fibrillation or palpitations, tachycardia, nervousness, tremor, or weight loss. Recent exposure to iodine, from contrast dyes or other sources, may precipitate or exacer bate thyrotoxicosis. The TSH level is low. The free T4 level may be normal or minimally increased; T3 is often elevated to a greater degree than T4. Thyroid scan shows heterogeneous uptake with multiple regions of increased and decreased uptake; 24-h uptake of radioiodine may not be increased but is usually in the upper normal range in the presence of the low TSH level. Prior to definitive treatment of the hyperthyroidism, ultrasound imaging should be performed to assess the presence of discrete nodules corresponding to areas of decreased uptake (“cold” nodules) (Fig. 397-3A). If present, fine-needle aspiration (FNA) may be indicated based on sonographic patterns and size cutoffs (see “Approach to the Patient with Thyroid Nodules”). The cytology results, if indeterminate or sus picious, may direct the therapy to surgery. TREATMENT Toxic Multinodular Goiter Antithyroid drugs normalize thyroid function and are particu larly useful in the elderly or ill patients with limited life span.

A B FIGURE 397-2 Sonographic patterns of thyroid nodules. A. High suspicion ultrasound pattern for thyroid malignancy ACR TI-RADS TR5 (hypoechoic solid nodule with irregular borders and punctate echogenic foci). B. Very low suspicion ultrasound pattern for thyroid malignancy ACR TI-RADS TR1 (spongiform nodule with microcystic areas comprising >50% of nodule volume). ACR TI-RADS, American College of Radiology Thyroid Imaging Reporting and Data System. Panel A Panel B FIGURE 397-3 Scintigraphic scans of thyroid nodules. I123 scan (anterior view) of right lower pole nonfunctioning “cold” nodule (A) in a euthyroid patient and left hyperfunctioning “hot” nodule (B) causing thyrotoxicosis with suppression of I123 uptake in the extranodular thyroid. (Courtesy of

Dan Pryma.)

In contrast to Graves' disease, spontaneous remission does not occur, and low-dose antithyroid drug therapy is well tolerated for years. Radioiodine is generally the treatment of choice; it treats areas of autonomy as well as decreasing the mass of the goiter by ablating the functioning nodules. Sometimes, however, a degree of autonomy may persist, presumably because multiple autonomous regions may emerge after others are treated, and further radio iodine treatment may be necessary. Surgery provides definitive treatment of underlying thyrotoxicosis as well as goiter. Patients should be rendered euthyroid using an antithyroid drug before operation.

Thyroid Nodular Disease and Thyroid Cancer CHAPTER 397 ■ ■HYPERFUNCTIONING SOLITARY NODULE A solitary, autonomously functioning thyroid nodule is referred to as toxic adenoma. The pathogenesis of this disorder has been unraveled by demonstrating the functional effects of mutations that stimulate the TSH-R signaling pathway. Most patients with solitary hyperfunc tioning nodules have acquired somatic, activating mutations in the TSH-R (Fig. 397-4). These mutations, located primarily in the recep tor transmembrane domain, induce constitutive receptor coupling to GSα, increasing cyclic adenosine monophosphate (AMP) levels and leading to enhanced thyroid follicular cell proliferation and func tion. Less commonly, somatic mutations are identified in GSα. These mutations, which are similar to those seen in McCune-Albright syndrome (Chap. 424) or in a subset of somatotrope adenomas (Chap. 392), impair guanosine triphosphate (GTP) hydrolysis, caus ing constitutive activation of the cyclic AMP signaling pathway. In most series, activating mutations in either the TSH-R or the GSα subunit genes are identified in >90% of patients with solitary hyper functioning nodules. Thyrotoxicosis is usually mild and is generally only detected when a nodule is >3 cm. The disorder is suggested by a subnormal TSH level; the presence of the thyroid nodule, often large enough to be palpable; and the absence of clinical features suggestive of Graves' disease or other causes of thyrotoxicosis. A thyroid scan provides a definitive diagnostic test, demonstrating focal uptake in the hyperfunctioning nodule and diminished uptake in the remainder of the gland, as activity of the normal thyroid is suppressed. TREATMENT Hyperfunctioning Solitary Nodule Radioiodine ablation is usually the treatment of choice. Because normal thyroid function is suppressed, 131I is concentrated in the

Extracellular domain TSH-R PART 12 Endocrinology and Metabolism

Transmembrane domains GSα AC Activating mutations Cell growth, differentiation Hormone synthesis cyclic AMP FIGURE 397-4 Activating mutations of the thyroid-stimulating hormone receptor (TSH-R). Mutations (*) that activate TSH-R reside mainly in transmembrane 5 and intracellular loop 3, although mutations have occurred in a variety of different locations. The effect of these mutations is to induce conformational changes that mimic TSH binding, thereby leading to coupling to stimulatory G protein (GSα) and activation of adenylate cyclase (AC), an enzyme that generates cyclic AMP. hyperfunctioning nodule with minimal uptake and damage to normal thyroid tissue. Relatively large radioiodine doses (e.g., 370– 1110 MBq [10–29.9 mCi] 131I) have been shown to correct thyrotox icosis in ~75% of patients within 3 months. Hypothyroidism occurs in <10% of those patients over the next 5 years. Surgical resection is also effective and is usually limited to lobectomy, thereby preserv ing thyroid function and minimizing risk of hypoparathyroidism or damage to the recurrent laryngeal nerves. Medical therapy using antithyroid drugs and beta blockers can normalize thyroid function but is not an optimal long-term

treatment. Using ultrasound guid ance, percutaneous radiofrequency ablation has been used success fully in some centers to ablate hyperfunctioning nodules, and this technique has also been used to reduce the size of nonfunctioning thyroid nodules. BENIGN LESIONS The various types of benign thyroid nodules are listed in Table 397-1. Benign nodules may be hyperplastic and reflect a combination of both macro- and microfollicular architecture, or they may be neoplastic, encapsulated adenomas that generally have a more monotonous microfollicular pattern. If the adenoma is composed of oncocytic follicular cells arranged in a follicular pattern, this is termed an oncocytic (formerly termed Hürthle cell) adenoma. Hyperplastic nodules generally appear as mixed cystic/solid or spongiform lesions on ultrasound. The definition of spongiform requires the presence of microcystic areas comprising >50% of the nodule volume, with the concept that this microcystic sonographic pattern recapitulates the histology of macrofollicles containing colloid (Fig. 397-2B). However, the majority of solid nodules (whether hypo-, iso-, or hyperechoic) are also benign. FNA, usually performed with ultrasound guidance, is the diagnostic procedure of choice to evaluate thyroid nodules (see the “Approach to the Patient with Thyroid Nodules” section). Pure thyroid cysts, <1% of all thyroid growths, consist of colloid and are benign as well. Cysts frequently recur, even after repeated

TABLE 397-1 WHO Classification of Thyroid Neoplasms Developmental abnormalities

1. Thyroglossal duct cyst
2. Other congenital thyroid abnormalities Follicular cell–derived neoplasms
3. Benign tumors a. Thyroid follicular nodular disease b. Follicular adenoma c. Follicular adenoma with papillary architecture d. Oncocytic adenoma of the thyroid
4. Low-risk neoplasms a. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features b. Thyroid tumors of uncertain malignant potential c. Hyalinizing trabecular tumor
5. Malignant neoplasms a. Follicular thyroid carcinoma b. Invasive encapsulated follicular variant papillary carcinoma c. Papillary thyroid carcinoma d. Oncocytic carcinoma of the thyroid e. Follicular-derived carcinomas, high-grade

i. Differentiated high-grade thyroid carcinoma

ii. Poorly differentiated thyroid carcinoma f. Anaplastic follicular cell–derived thyroid carcinoma Thyroid C-cell–derived carcinoma

1. Medullary thyroid carcinoma Mixed medullary and follicular cell–derived carcinomas Salivary gland–type carcinomas of the thyroid
2. Mucoepidermoid carcinoma of the thyroid
3. Secretory carcinoma of salivary gland type Thyroid tumors of uncertain histogenesis
4. Sclerosing mucoepidermoid carcinoma with eosinophilia
5. Cribriform morular thyroid carcinoma Thymic tumors within the thyroid
6. Thymoma family
7. Spindle epithelial tumor with thymus-like elements
8. Thymic carcinoma family Embryonal thyroid neoplasms
9. Thyroblastoma Abbreviation: WHO, World Health Organization. Source: Reprinted from International Agency for Research on Cancer, WHO Classification of Tumours,

https://whobluebooks.iarc.fr/structures/ endocrine-and-neuroendocrine-tumours/ aspiration, and may require surgical excision if they are large. Ethanol ablation to sclerose the cyst has been used successfully for patients who are symptomatic. TSH suppression with LT4 therapy does not decrease thyroid nodule size in iodine-sufficient populations. However, if there is relative iodine deficiency, both iodine and LT4 therapy have been demonstrated to decrease nodule volume. If LT4 is administered in this situation, the TSH should be maintained at or just below the lower limit of normal, but not frankly suppressed. If the nodule has not decreased in size after 6–12 months of therapy, treatment should be discontinued because little benefit is likely to accrue from long-term treatment; the risk of iatrogenic subclinical thyrotoxicosis should also be considered.

THYROID CANCER Thyroid carcinoma is the most common malignancy of the endocrine system. Malignant tumors derived from the follicular epithelium are classified according to histologic features. Differentiated tumors, such as papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC), are often curable, and the prognosis is good for patients identified with early-stage disease. In contrast, anaplastic thyroid cancer (ATC) is aggressive, responds poorly to treatment, and is associated with a bleak prognosis. Over the past 30 years, the incidence of thyroid cancer has increased from 4.9 to >15 cases per 100,000 individuals in the United States. However, disease-specific mortality has only minimally increased. The increased incidence is predominantly attributable to small T1 papillary cancer tumors (<2 cm) and has led experts to consider that thyroid cancer is being overdiagnosed, suggesting that cancers are being detected that would otherwise be unlikely to harm a patient. The concept of cancer overdiagnosis is predicated upon the presence of a disease reservoir (the autopsy prevalence of PTC is ~25%), activi ties leading to disease detection (increased diagnostic imaging with incidental detection of nodules), and a mismatch in the directional rate between diagnosis and mortality (thyroid cancer disease-specific mortality not changed in 40 years). Similar trends have been observed worldwide, especially in countries with a higher proportion of privately financed health care, leading to increased resource utilization includ ing imaging. The 20-year disease-specific mortality for low-risk thy roid cancer is 1%. Fortunately, epidemiologic data in the United States document a decrease in new thyroid cancer diagnoses (62,450 cases in 2015 and 43,720 cases in 2023), and this trend correlates with the implementation of evidence-based guidelines that recommend higher size thresholds for nodule FNA. Current trends in thyroid cancer care focus on (1) avoiding over diagnosis by limiting FNA by sonographic risk stratification with size cutoffs; (2) limiting surgery, radioiodine, and subsequent surveillance for low-risk tumors; and (3) identifying patients at higher recurrence risk for more aggressive treatment and monitoring. Prognosis is gen erally worse in older persons (>65 years). Thyroid cancer is twice as common in women as men, but male gender is associated with a worse prognosis. Additional important risk factors include a history of child hood (before age 18) head or neck irradiation, evidence for local tumor fixation or gross metastatic involvement of lymph nodes, and the pres ence of distant metastases (Table 397-2). Several unique features of thyroid cancer facilitate its management: (1) thyroid nodules are amenable to biopsy by FNA; (2) iodine radioisotopes can be used to diagnose (123I and 131I) and potentially treat (131I) differen tiated thyroid cancer, reflecting the unique uptake of this anion by the thyroid gland; and (3) serum markers allow the detection of residual or recurrent disease, including the use of Tg levels for PTC FTC and onco cytic carcinoma and calcitonin for medullary thyroid cancer (MTC). ■ ■CLASSIFICATION Thyroid neoplasms can arise in each of the cell types that populate the gland, including thyroid follicular cells, calcitonin-producing C cells, TABLE 397-2 Risk Factors for Thyroid

Carcinoma in Patients with Thyroid Nodule from History and Physical Examination History of head and neck irradiation before the age of 18, including mantle radiation for Hodgkin’s disease and brain radiation for childhood leukemia or other cranial malignancies Exposure to ionizing radiation from fallout in childhood or adolescence Age <20 or >65 years Rapidly enlarging neck mass Male gender Family history of papillary thyroid cancer in two or more first-degree relatives, MEN 2, or other genetic syndromes associated with thyroid malignancy (e.g., Cowden’s syndrome, familial adenomatous polyposis, Carney complex, PTEN [phosphatase and tensin homolog] hamartoma tumor) Vocal cord paralysis, hoarse voice Nodule fixed to adjacent structures Lateral cervical lymphadenopathy (ipsilateral to the nodule) 18FDG or Ga-68 Dotatate PET avidity Abbreviations: FDG, fluorodeoxyglucose; MEN, multiple endocrine neoplasia; PET, positron emission tomography.

lymphocytes, and stromal and vascular elements, as well as metastases from other sites (Table 397-1). The American Joint Committee on Cancer (AJCC) staging system using the tumor, node, metastasis (TNM) classi fication is most commonly used. This system classifies different types of thyroid cancers (papillary, follicular, poorly differentiated, oncocytic cell, or anaplastic) based upon: 1) tumor size and extrathyroidal invasion; 2) regional lymph node metastases; and 3) distant metastases.1

■ ■PATHOGENESIS AND GENETIC BASIS Radiation Early studies of the pathogenesis of thyroid cancer focused on the role of external radiation, which predisposes to chromosomal breaks, leading to genetic rearrangements and loss of tumor-suppressor genes. External radiation of the mediastinum, face, head, and neck region was administered in the past to treat an array of conditions, including acne and enlargement of the thymus, tonsils, and adenoids. Radiation exposure increases the risk of benign and malig nant thyroid nodules, is associated with multicentric cancers, and shifts the incidence of thyroid cancer to an earlier age group. Radiation from nuclear fallout also increases the risk of thyroid cancer through absorp tion of radioactive iodine isotopes. Children seem more predisposed to the effects of radiation than adults. Thyroid Nodular Disease and Thyroid Cancer CHAPTER 397 TSH and Growth Factors Many differentiated thyroid cancers express TSH receptors and, therefore, remain responsive to TSH. Higher serum TSH levels, even within normal range, are associated with increased thyroid cancer risk in patients with thyroid nodules. These observations provide the rationale for T4 suppression of TSH in patients with thyroid cancer. Residual expression of TSH receptors also allows TSH-stimulated uptake of 131I therapy (see below). Oncogenes and Tumor-Suppressor Genes Thyroid cancers are monoclonal in origin, consistent with the idea that they originate as a consequence of mutations that confer a growth advantage, or resistance to cell death, to a single progenitor cell. In addition to increased rates of proliferation, some thyroid cancers exhibit impaired apoptosis and features that enhance invasion, angiogenesis, and metastasis. Thyroid neoplasms have been analyzed for a variety of genetic alterations, but without clear evidence of an ordered acquisition of somatic mutations as they progress from the benign to the malignant state. On the other hand, certain mutations, such as RET/PTC and PAX8-PPARγ1 rear rangements, are relatively specific for thyroid neoplasia. As described above, activating mutations of the TSH-R and the GSα subunit are associated with autonomously functioning nodules. Muta tions in the enhancer of zeste homolog 1 (EZH1), which plays a role in chromatin remodeling, are also seen in about a quarter of autonomous nodules. Although these mutations induce thyroid cell growth, this type of nodule is almost always benign, likely because they drive dif ferentiation pathways. Activation of the RET-RAS-BRAF signaling pathway is seen in up to 70% of PTCs, although the types of mutations are

heterogeneous. A variety of rearrangements involving the RET gene on chromosome 10 bring this receptor tyrosine kinase under the control of other promot ers, leading to receptor overexpression. RET rearrangements occur in 15% of PTCs in different series and were observed with increased fre quency in tumors developing after the Chernobyl radiation accident. Rearrangements in PTC have also occurred for another tyrosine kinase gene, TRK1, which is located on chromosome 1. BRAF V600E muta tions are a common genetic alteration, occurring in up to 60% of PTC. These mutations activate the kinase, which stimulates the mitogenactivated protein kinase (MAPK) cascade. RAS mutations, which also stimulate the MAPK cascade, are found in ~15% of thyroid neoplasms (NRAS > HRAS > KRAS), including both PTC follicular variant and FTC. Of note, simultaneous RET, BRAF, and RAS mutations rarely occur in the same tumor, suggesting that activation of the MAPK 1RM Tuttle et al: Updated American Joint Committee on Cancer/Tumor-NodeMetastasis Staging System for Differentiated and Anaplastic Thyroid Cancer (Eighth Edition): What changed and why? Thyroid 27:751, 2017.

cascade is critical for tumor development, independent of the step that initiates the cascade. Activation of the phosphatidylinositol 3-kinase (PI3K) pathway, often by deletion of the PTEN phosphatase gene, also occurs in both differentiated thyroid cancers.

BRAF and RAS mutations also occur in FTCs. In addition, a rear rangement of the thyroid developmental transcription factor PAX8 with the nuclear receptor PPARγ is identified in a significant fraction of FTCs, usually independent of RAS pathway mutations. Overall, ~70% of follicular cancers have mutations or genetic rearrangements. Loss of heterozygosity of 3p or 11q, consistent with deletions of tumor-suppressor genes, is also common in FTCs. Upregulation and downregulation of various microRNAs also influence gene expression patterns in both differentiated and dedifferentiated thyroid cancers. PART 12 Endocrinology and Metabolism Oncocytic tumors, which contain large numbers of mitochondria, are characterized by mutations in mitochondrial genes, primarily encoding enzymes in the electron transport chain. They also exhibit chromosomal copy number alterations and near haploidization. Most of the mutations seen in differentiated thyroid cancers have also been detected in ATCs. TERT promoter mutations occur in <10% of differentiated PTCs but are more common in ATC. BRAF mutations are seen in up to 50% of ATCs. Mutations in CTNNB1, which encodes β-catenin, occur in about two-thirds of ATCs, but not in PTC or FTC. Mutations of the tumor-suppressor P53 also play an important role in the development of ATC. Because P53 plays a role in cell-cycle surveillance, DNA repair, and apoptosis, its loss may contribute to the rapid acquisi tion of genetic instability as well as poor treatment responses (Chap. 77). MTC, when associated with multiple endocrine neoplasia (MEN) type 2, harbors an inherited mutation of the RET gene. Unlike the rearrangements of RET seen in PTC, the mutations in MEN 2 are point mutations that induce constitutive activity of the tyrosine kinase (Chap. 400). MTC is preceded by hyperplasia of the C cells, raising the likelihood that as-yet-unidentified “second hits” lead to cellular transformation. A subset of ~40% of sporadic MTC contains somatic mutations that activate RET. Molecular diagnostics are being used more commonly in the clini cal management of thyroid nodules, particularly to distinguish benign from malignant lesions after FNA and to reduce the number of diag nostic surgeries for indeterminate nodules. These tools are now offered as diagnostic panels by specialized referral laboratories. The panels also distinguish parathyroid and medullary nodules from thyroid follicular cell–derived lesions. ■ ■WELL-DIFFERENTIATED THYROID CANCER Papillary PTC is the most common type of thyroid cancer, account ing for 80–85% of well-differentiated thyroid malignancies. Micro scopic PTC is present in up to 25% of thyroid glands at

autopsy, but most of these lesions are very small (several millimeters) and are not clinically significant. Characteristic cytologic features of PTC help make the diagnosis by FNA or after surgical resection; these include large, clear nuclei with powdery chromatin (described as an “Orphan Annie eye” appearance) with nuclear grooves and prominent nucleoli. The histologic finding of these cells arranged in either papillary struc tures or follicles distinguishes the classic and follicular variants of PTC, respectively. There are several subtypes of papillary thyroid cancer. The more differentiated classic and follicular variants are likely to have an indolent course in the absence of angioinvasion or metastatic adenopa thy. The aggressive variants (tall cell, columnar cell, hobnail, poorly differentiated) require more intensive therapy and closer follow-up. Recently, a subtype previously known as the encapsulated PTC follicu lar variant, without capsular or angioinvasion, is no longer considered malignant and has been renamed noninvasive follicular thyroid neo plasm with papillary-like nuclear features (NIFTP). PTC may be multifocal and invade locally within the thyroid gland as well as through the thyroid capsule and into adjacent structures in the neck. It has a propensity to spread via the lymphatic system but can metastasize hematogenously as well, particularly to bone and lung. Because of the relatively slow growth of the tumor, a significant burden of pulmonary metastases may accumulate, sometimes with

1.0 Disease-specific survival probability 0.8 0.6 p <0.001 0.4 Stage = I Stage = II Stage = III Stage = IV 0.2 0.0

Time from diagnosis (months)

108 120 132 FIGURE 397-5 Unadjusted disease-specific survival curves for patients with papillary thyroid cancer in the American Joint Commission on Cancer/Union for International Cancer Control eighth edition TNM staging system. (Reproduced with permission from LN Pontius et al: Projecting survival in papillary thyroid cancer: A comparison of the seventh and eighth editions of the American Joint Commission on Cancer/Union for International Cancer Control Staging Systems in two contemporary national patient cohorts. Thyroid 27:1408, 2017. The publisher for this copyrighted material is MaryAnn Liebert, Inc. publishers.) remarkably few symptoms. The prognostic implication of lymph node spread depends on the volume of metastatic disease. Micrometastases, defined as <2 mm of cancer in a lymph node, do not affect prognosis. However, gross metastatic involvement of multiple 2- to 3-cm lymph nodes indicates a 25–30% chance of recurrence and may increase mortality in older patients. Most papillary cancers are identified in the early stages (>95% stages I or II) and have an excellent prognosis, with survival curves similar to expected survival (Fig. 397-5). Mortality is markedly increased in stage IV disease, especially in the presence of distant metastases (stage IVB), but this group comprises only about 1% of patients. The treatment of PTC is described below. Follicular The incidence of FTC varies widely in different parts of the world; it is more common in iodine-deficient regions. Currently, FTC accounts for only about 5% of all thyroid cancers diagnosed in the United States. FTC is difficult to diagnose by FNA because the dis tinction between benign and malignant follicular neoplasms requires histology because the nuclear features of follicular adenomas and car cinomas do not differ. Rather, follicular carcinoma is diagnosed by the presence of capsular and/or vascular invasion. Follicular carcinomas with only capsular invasion have a very low risk of metastasis, and lobectomy alone suffices. Angioinvasive FTC is more aggressive and may metastasize to bone, lung, and the central nervous system. Mor tality rates associated with angioinvasive FTC are less favorable than for PTC, in part because a larger proportion of patients present with stage IV disease. Poor prognostic features

include distant metastases, age >55 years, primary tumor size >4 cm, and the presence of marked vascular invasion. TREATMENT Surgery for Well-Differentiated Thyroid Cancer All well-differentiated thyroid cancers >1–1.5 cm (T1b or larger) should be surgically excised. Active surveillance is an option for small (up to 1.5 cm) intrathyroidal micropapillary thyroid cancers without cervical lymph node metastases, extrathyroidal extension, or location near the posterior thyroid capsule (near the recurrent laryngeal nerve). In addition to removing the primary lesion, surgery allows accurate histologic diagnosis and staging. Because there is no compelling evidence that bilateral thyroid surgery improves survival, the initial surgical procedure may be either a unilateral (lobectomy) or bilateral (near-total thyroidectomy) pro cedure for patients with intrathyroidal cancers >1 cm and <4 cm

(T1b and T2 tumors) in the absence of metastatic disease and after a careful sonographic evaluation for metastatic cervical adenopathy. For patients at high risk for recurrence, bilateral surgery allows administration of radioiodine for remnant ablation and potential treatment of iodine-avid metastases, if indicated, as well as for monitoring of serum Tg levels. Therefore, near-total thyroidectomy is appropriate in the presence of metastases or clinical evidence of extrathyroidal invasion and for most tumors >4 cm. In addition, for patients found to have a high-risk tumor after lobectomy based upon aggressive pathology features (e.g., vascular invasion or a less differentiated subtype), completion surgery should be performed to allow for effective radioiodine administration. Surgical complica tion rates are acceptably low if the surgeon is highly experienced in the procedure. Preoperative sonography should be performed in all patients to assess the central and lateral cervical lymph node compartments for suspicious adenopathy, which if present, should undergo FNA and be removed, as indicated, at surgery. TSH SUPPRESSION THERAPY Because most tumors are still TSH-responsive, LT4 suppression of TSH has been mainstay of thyroid cancer treatment. The degree of TSH suppression should be individualized based on a patient’s risk of recurrence. It should be adjusted over time as surveillance blood tests and imaging confirm absence of disease or, alternatively, indicate pos sible residual/recurrent cancer. For patients at low risk of recurrence, TSH should be maintained in the lower normal limit (0.5–2.0 mIU/L). For patients either at intermediate or high risk of recurrence, TSH levels should be kept to 0.1–0.5 mIU/L and <0.1 mIU/L, respectively, if there are no strong contraindications to mild thyrotoxicosis. TSH should be <0.1 mIU/L for those with known metastatic disease. RADIOIODINE TREATMENT After near-total thyroidectomy, <1 g of thyroid tissue remains in the thyroid bed. Postsurgical radioablation of the remnant thyroid eliminates residual normal thyroid, facilitating the use of Tg deter minations. In addition, well-differentiated thyroid cancer often incorporates radioiodine, although less efficiently than normal thyroid follicular cells. Radioiodine uptake is determined primar ily by expression of the NIS and is stimulated by TSH, requiring expression of the TSH-R. The retention time for radioactivity is influenced by the extent to which the tumor retains differentiated functions such as iodide trapping and organification. Consequently, for patients at higher risk of recurrence and for those with known distant metastatic disease, 131I therapy may provide an adjuvant role and potentially treat residual tumor cells. Indications Not all patients benefit from radioiodine therapy. Neither recurrence nor survival rates are improved in stage I patients with T1 tumors (≤2 cm) confined to the thyroid. No benefit has been demonstrated for larger (>2 cm but <4 cm) lowrisk tumors. However, in higher risk patients (larger tumors, more aggressive variants of papillary cancer, tumor vascular invasion, extrathyroidal invasion, presence of large-volume lymph node metastases), radioiodine may reduce recurrence and may increase survival for older patients. 131I Thyroid Ablation and Treatment As noted above, the decision to use 131I for thyroid ablation

should be coordinated with the sur gical approach, because radioablation is much more effective when there is minimal remaining normal thyroid tissue. Radioiodine is administered after iodine depletion (patient follows a low-iodine diet for 1–2 weeks) and in the presence of elevated serum TSH levels to stimulate uptake of the isotope into both the remnant and potentially any residual tumor. To achieve high serum TSH levels, there are two approaches. A patient may be withdrawn from thy roid hormone so that endogenous TSH is secreted and, ideally, the serum TSH level is >25 mIU/L at the time of 131I therapy. A typical strategy is to treat the patient for several weeks postoperatively with liothyronine (25 μg qd or bid), followed by thyroid hormone withdrawal for 2 weeks. Alternatively, recombinant human TSH

(rhTSH) is administered as two daily consecutive injections (0.9 mg) with administration of 131I 24 h after the second injection. The patient can continue to take LT4 and remains euthyroid. Both approaches have equal success in achieving remnant ablation.

A pretreatment scanning dose of 131I (usually 111 MBq [3 mCi]) or 123I (74 MBq [2 mCi]) can reveal the amount of residual tis sue and provides guidance about the dose needed to accomplish ablation. However, because of concerns about radioactive “stun ning” that impairs subsequent treatment, there is a trend to avoid pretreatment scanning with 131I and use either 123I or proceed directly to ablation, unless there is suspicion that the amount of residual tissue will alter therapy or that there is distant metastatic disease. In the United States, outpatient doses of up to 6475 MBq (175 mCi) can be given at most centers. The administered dose depends on the indication for therapy, with lower doses of 1100 MBq (30 mCi) given for remnant ablation but higher doses of up to 5500 MBq (150 mCi) reserved for use as adjuvant therapy when residual disease is suspected or present. Whole-body scanning (WBS) following radioiodine treatment is used to confirm the 131I uptake in the remnant and to identify possible metastatic disease. Thyroid Nodular Disease and Thyroid Cancer CHAPTER 397 Surveillance Testing Serum thyroglobulin (Tg) is a sensitive marker of residual/recurrent thyroid cancer after ablation of the residual postsurgical thyroid tissue. Current Tg assays have func tional sensitivities as low as 0.1 ng/mL, as opposed to older assays with functional sensitivities of 1–2 ng/mL, reducing the number of patients with truly undetectable serum Tg levels. Because the vast majority of PTC recurrences are in cervical lymph nodes, a neck ultrasound should be performed about 6 months after thyroid abla tion; ultrasound has been shown to be more sensitive than WBS in this scenario. In low-risk patients who have no clinical evidence of residual disease after ablation, negative cervical sonography, and a basal Tg <0.2 ng/mL on LT4, the risk of structural recurrence is <3% at 5 years, and the frequency of follow-up testing can be decreased to annual TSH and Tg testing, with only periodic ultrasound examina tion. The serum TSH should be maintained in the lower half of the normal range. The use of WBS for thyroid cancer surveillance is reserved for patients with known iodine-avid metastases or those with elevated serum thyroglobulin levels and negative imaging with ultrasound, chest CT, neck cross-sectional imaging, and positron emission tomography (PET) CT who may require additional 131I therapy. In addition to radioiodine, external beam radiotherapy is also used to treat gross residual neck disease or specific metastatic lesions, particularly when they cause bone pain or threaten neuro logic injury (e.g., vertebral metastases). New Potential Therapies Kinase inhibitors target pathways known to be active in thyroid cancer, including the RAS, BRAF, RET, EGFR, VEGFR, and angiogenesis pathways. Treatment has been shown to stabilize progressive metastatic disease that is refractory to radioiodine therapy, although only one study has demonstrated improved survival. Given the significant associated toxicities and the need for ongoing therapy, patient

selection is critical to limit systemic therapy to those with significant morbid ity risk. The American Thyroid Association guidelines recommend active surveillance for asymptomatic patients with metastatic tumors between 1 and 2 cm and then intervention as the rate of tumor growth increases. In addition, based on genetic analyses of metastases, mutation-selective kinase inhibitors are now being used. In addition to multikinase inhibitors, new therapies target tumor-specific mutational changes including BRAF V600E point mutations and NTRK and RET gene fusions. Immune checkpoint inhibitors have also shown efficacy for some thyroid cancers with high tumor mutation burden (TMB-H). Ongoing trials are also exploring whether differentiation protocols, targeting the MAPK pathway, might enhance radioiodine uptake and efficacy.

■ ■ANAPLASTIC AND OTHER FORMS OF THYROID CANCER

Anaplastic Thyroid Cancer As noted above, ATC is a poorly differentiated and aggressive cancer. The prognosis is poor, and most patients die within 6 months of diagnosis. Because of the undifferentiated state of these tumors, the uptake of radioiodine is usually negligible, but it can be used therapeutically if there is resid ual uptake. Chemotherapy has been attempted with multiple agents, including anthracyclines and paclitaxel, but it is usually ineffective. External beam radiation therapy can be attempted and continued if tumors are responsive. Both multitargeted and mutation-directed kinase inhibitors are in clinical trials and may prolong survival by a few months. Thyroid Lymphoma Lymphoma in the thyroid gland often arises in the background of Hashimoto’s thyroiditis. A rapidly expanding thyroid mass suggests the possibility of this diagnosis. Diffuse large-cell lymphoma is the most common type in the thyroid. Biopsies reveal sheets of lymphoid cells that can be difficult to dis tinguish from small-cell lung cancer or ATC. These tumors are often highly sensitive to external radiation. Surgical resection should be avoided as initial therapy because it may spread disease that is oth erwise localized to the thyroid. If staging indicates disease outside of the thyroid, treatment should follow guidelines used for other forms of lymphoma (Chap. 113). PART 12 Endocrinology and Metabolism ■ ■MEDULLARY THYROID CARCINOMA MTC can be sporadic or familial and accounts for ~5% of thyroid can cers. There are three familial forms of MTC: MEN 2A, MEN 2B, and familial MTC without other features of MEN (Chap. 400). In general, MTC is more aggressive in MEN 2B than in MEN 2A, and familial MTC is more aggressive than sporadic MTC. Elevated serum calcito nin provides a marker of residual or recurrent disease. All patients with MTC should be tested for RET mutations, because genetic counseling and testing of family members can be offered to those individuals who test positive for mutations. The management of MTC is primarily surgical. Prior to surgery, pheochromocytoma should be excluded in all patients with a RET mutation. Unlike tumors derived from thyroid follicular cells, these tumors do not take up radioiodine. External radiation treatment and targeted kinase inhibitors may provide palliation in patients with advanced disease (Chap. 400). APPROACH TO THE PATIENT Thyroid Nodules Palpable thyroid nodules are found in ~5% of adults, but the preva lence varies considerably worldwide. Given this high prevalence rate, practitioners may identify thyroid nodules on physical exami nation. However, the increased usage of diagnostic medical imaging (e.g., carotid ultrasound, cervical spine MRI) has led to an increased frequency of incidental nodule detection, accounting for the major ity of patients currently presenting for nodule evaluation. The main goal of this evaluation is to identify, in a cost-effective manner, the small subgroup of individuals with malignant lesions that have the potential to be clinically significant. Nodules are more common in iodine-deficient areas, in women, and with aging. Most palpable nodules are >1 cm in diameter, but the ability to feel a nodule is influenced by its location within the gland

(superficial vs deeply embedded), the anatomy of the patient's neck, and the experience of the examiner. More sensitive methods of detection, such as CT, thyroid ultrasound, and pathologic studies, reveal thyroid nodules in up to 50% of glands in individuals aged

> 50 years. The presence of these thyroid incidentalomas has led to much debate about how to detect nodules and which nodules to investigate further. An approach to the evaluation of thyroid nodules detected by either palpation or imaging is outlined in Fig. 397-6. Most patients

with thyroid nodules have normal thyroid function tests. None theless, thyroid function should be assessed by measuring a TSH level, which may be suppressed by one or more autonomously functioning nodules. If the TSH is suppressed, a radionuclide scan is indicated to determine if the identified nodule is "hot," as lesions with increased uptake are almost never malignant and FNA is unnecessary (Fig. 397-3B). Otherwise, the next step in evaluation is performance of a thyroid ultrasound for three reasons: (1) For nodules detected on physical examination, ultrasound will confirm if the palpable nodule is indeed a nodule. About 15% of "palpable" nodules are not confirmed on imaging, and therefore no further evaluation is required. (2) Ultrasound will assess if there are addi tional nonpalpable nodules for which FNA may be recommended based on imaging features and size. (3) Ultrasound will characterize the imaging pattern of the nodule, which, combined with the nod ule's size, facilitates decision-making about FNA. There are several validated risk stratification systems (RSS) for sonographic imaging of thyroid nodules (American College of Radiology [ACR] Thyroid Imaging Reporting and Data System [TI-RADS], American Thy roid Association, European Thyroid Association [EU-TIRADS], among others). These demonstrate consistent risk estimates for thyroid cancer based on certain sonographic patterns. All provide size cutoff recommendations for nodule FNA based on sonographic patterns, with lower size cutoffs for nodules with more suspicious ultrasound patterns, but the specific size cutoff criteria differ among the RSS. Not surprisingly, the RSSs with lower size cutoffs have higher sensitivity and lower specificity for thyroid cancer diagnosis than those with higher cutoffs. Nevertheless, all have been shown to reduce unnecessary FNAs by at least 45%, in part due to the recom mendation not to perform FNA for spongiform nodules. ACR TIRADS is currently the most widely used RSS in the United States, and nodules are classified from TR1 to TR5 (Fig. 397-1). For example, a spongiform nodule (TR1, Fig. 397-2B) has a <3% chance of cancer, and observation rather than FNA is generally recommended by all RSSs, whereas 10–20% of solid hypoechoic nodules with smooth borders (TR4) are malignant and FNA is recommended at size cutoffs ranging from 1 to 1.5 cm. All the RSSs recommend FNA at 1 cm for the highest suspicion pattern nodule, TR5 (Figs. 397-1 and 397-2A). Given what is known about the prevalence and generally indolent behavior of small thyroid cancers <1 cm, none of the RSSs recommend routine FNA for any nodule <1 cm unless metastatic cervical lymph nodes are present. FNA biopsy, ideally performed with ultrasound guidance, is the best diagnostic test when performed by physicians familiar with the procedure and when the results are interpreted by experienced cyto pathologists. The technique is particularly useful for detecting PTC. However, the distinction between benign and malignant follicular patterned lesions is often not possible using cytology alone because of the absence of characteristic nuclear features in follicular carci noma. Using the current ultrasound RSS for FNA decision-making, FNA biopsies yield the following spectrum of cytology diagnoses: 50–60% benign,

5% malignant or suspicious for malignancy, 5–7% nondiagnostic or yielding insufficient material for diagnosis, and 25–40% indeterminate. The Bethesda System is now widely used to provide more uniform terminology for reporting thyroid nodule FNA cytology results. This six-tiered classification system (newest version 3) with the respective estimated malignancy rates is shown in Table 397-3. Importantly, because NIFTP can only be diagnosed by surgical pathology, NIFTP is included in the malignancy esti mates. Specifically, the Bethesda System subcategorized cytology specimens previously labeled as indeterminate into three catego ries: atypia undetermined significance (AUS), follicular neoplasm (FN), and suspicious for malignancy (SFM). Cytology results indicative of malignancy generally mandate surgery, after performing preoperative sonography to evaluate the cervical lymph nodes. Nondiagnostic cytology specimens most often result from cystic lesions but may also occur in fibrous longstanding nodules or very vascular nodules where a longer needle

EVALUATION OF THYROID NODULES DETECTED BY PALPATION OR IMAGING History, physical examination, TSH Normal or high TSH Low TSH Diagnostic US with LN assessment Nodule not functioning Radionuclide scanning Nodule(s) detected on US Do FNA based upon US imaging features and size Results of FNA cytology Nondiagnostic Nondiagnostic Repeat US-guided FNA Malignant Bethesda System Cytology Reporting Suspicious for PTC Follicular neoplasm Consider molecular testing Surgery if indicated Atypia or follicular lesion of undetermined significance (AUS/FLUS) Benign Follow FIGURE 397-6 Approach to the patient with a thyroid nodule. See text and references for details. FNA, fine-needle aspiration; LN, lymph node; PTC, papillary thyroid cancer; Rx, therapy; TSH, thyroid-stimulating hormone; US, ultrasound. dwell time may result in a hemorrhagic specimen. Ultrasoundguided FNA is indicated when a repeat FNA is necessary. Repeat FNA will yield a diagnostic cytology in ~50% of cases. Given the low false-negative rate of a benign cytology (<3%), benign nodules with a lower suspicion sonographic pattern (TR2, TR3, TR4) can be followed. Those with more worrisome ultrasound features, espe cially TR5 nodules, should undergo repeat FNA because of a higher likelihood of a missed malignancy. The use of LT4 to suppress TABLE 397-3 Bethesda Classification for Thyroid Cytology Version 3 RISK OF MALIGNANCY

(INCLUDING NIFTP)

MEAN % (RANGE) DIAGNOSTIC CATEGORY I. Nondiagnostic or unsatisfactory 13 (5–20) II. Benign 4 (2–7) III. Atypia of unknown significance (AUS) 22 (13–30) IV. Follicular neoplasm (FN) 30 (23–34) V. Suspicious for malignancy (SFM) 74 (67–83) VI. Malignant 97 (97–100) Abbreviation: NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

Thyroid Nodular Disease and Thyroid Cancer CHAPTER 397 Hyperfunctioning nodule Evaluate and Rx for hyperthyroidism Close follow-up or surgery Surgery Repeat US-guided FNA or consider molecular testing Surgery if indicated serum TSH is not effective in shrinking nodules in iodine-replete populations, and therefore, LT4 suppression should not be used. The three indeterminate cytology classifications introduced by the Bethesda System are associated with different risks of malignancy (Table 397-3). For nodules with suspicious for malignancy cytology, surgery is recommended after ultrasound assessment of cervical lymph nodes. Options to be discussed with the patient include lobectomy versus total thyroidectomy. On the other hand, the majority of nodules with AUS and FN cytology results are benign; the range of malignancy (ROM) var ies from 13 to 34%. The traditional approach for these patients is diagnostic lobectomy for histopathologic diagnosis. Therefore, many patients undergo surgery for benign nodules. Over the past decade, the uncertainty about the ROM for indeterminate cytology nodules has been the driver for the

development of molecular test ing, which can better differentiate benign from malignant nodules. Based on results from next-generation sequencing, which includes point mutations, small insertions/deletions, and gene fusions, as well as results from microRNA analyses and gene expression, the cur rent validated and commercially available molecular tests combine these techniques with the following two goals: (1) risk stratification of thyroid nodules based on a positive result; and (2) reduction in cancer risk to an acceptable level for nonsurgical surveillance based

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